

EXHIBIT

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Wien Klin Wochenschr 2002 Aug 30;114(15-16):671-7 Related Articles, Links

Tubular apoptosis in the pathophysiology of renal disease.

Hauser P, Oberbauer R.

Abteilung fur Nephrologie, Universitätsklinik für Innere Medizin, Universität Wien,
Vienna, Austria.

Apoptosis of renal tubular epithelial cells plays a major role in acute renal failure. Several external and internal signals can induce apoptosis, which is then effectuated via several pathways. These pathways are either the FAS/FAS-L pathway and downstream MAPK (mitogen-activated protein kinases) and JNK (c-Jun N-terminal kinase) signal transduction, or the RANK/RANK-L (receptor activator of NF_kB) pathway via activation of the caspase cascade. Other pathways, especially for apoptosis induction by toxins, include the mitochondrial permeability transition pore activation and Bcl-2 superfamily member differential regulation. An important final, irreversible branch of these pathways is the release of cytochrome c from the mitochondria, leading to nuclear fragmentation. Therapeutic interventions of acute tubular injury focus on the prevention of apoptosis by either modulation of the balance of the bcl-2 family or by selectively blocking angiotensin receptors. It is not clear yet, which receptor blockade or combination of receptor blockers are most effective in apoptosis prevention. In chronic renal failure, tubular apoptosis has been found in biopsies from polycystic kidneys, but not in a quantitatively meaningful amount in other chronic human renal diseases. On the other hand, given the short half-life of apoptotic cells of few hours, even low numbers over time might turn out to be important modulators of chronic kidney disease, which are characterized by tubular cell loss. Potential therapeutic interventions to prevent tubular apoptosis in chronic renal disease include angiotensin system inhibition, whereby the angiotensin II AT2 receptor blockade seems more promising in apoptosis inhibition than the inhibition of other receptor subtypes.